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THE STUDIES ON GUI-LIN-TANG IN THE TREATMENT OF RHEUMATOID ARTHRITIS

Chi-Wen Chou, Ming-Tsuen Hsieh, Ho-Chan Chen, Lii-Yih

The Department of Orthopedics and Institute of Chinese Pharmaceutical Sciences, Peikan Hospital and China Medical College, Taichung, Taiwan, R.O.C.

Seventy-two patients with definite or classic rheumatoid arthritis were treated with Gui-Lin-Tang and 44 patients (33 females, 11 males) completed the study. Thirty-four patients were treated with Gui-Lin-Tang alone. Ten patients were treated with Gui-Lin-Tang in addition to gold or D-penicillamine. All the patients tolerated the drug and had an averaged 77.2 days follow-up. Twelve patients (27.2%) were markedly improved, 22 (50%) moderately or slightly improved, and 10 (22.8%) unimproved. IgG, IgA and IgM values were decreased in 61.5% of the patients treated with Gui-Lin-Tang alone.

INTRODUCTION

The etiology of rheumatoid arthritis is unknown, but the pathogenesis of rheumatoid arthritis can be considered as immunological events induced by the etiological factor and inflammatory reaction followed.[1] The detection of large numbers of T-lymphocytes in synovial and the presence of lymphokines in synovial fluid imply a role for cell-mediated immunity.[2] Non-steroid anti-inflammatory and disease-modifying drugs like gold and D-penicillamine are mostly used singly or in combination in treatment. But for patients using these drugs there are many restrictions due to their severse adverse side effects.[3,4,5]

Chinese herbal drugs have been used to treat many kinds of inflammatory disease since ancient times. Gui-Zhi-Tang, found by Chung-Ching Chang in about 1800 years ago, is a basic Chinese herb formula for acute inflammatory disease.[6] Many formulas have been developed from Gui-Zhi-Tang for treating arthritis. Gui-Zhi-Tang consists of five herbs including Cinnamomi Ramulus, Paeoniae Radix, Zingiberis Rhizoma, Zizyphi Fructus and Glycyrrhizae Radix. The Gui-Lin-Tang used in this study was modified by adding Aconiti Tuber, Atractylodis Rhizoma and Poria. This Gui-Lin-Tang has been shown in animal and human studies to posses analgesic, anti-inflammatory and immune modulating effects.[7]

The purpose of the present study was to demonstrate the effects of Gui-Lin-Tang in patients with rheumatoid arthritis. The clinical improvements as well as certain changes in laboratory parameters, especially erythrocyte sedimentation rate and the titer of

immune globulin were evaluated. The adverse side effects and toxicity were also evaluated. Our experience with Gui-Lin-Tang in the treatment of rheumatoid arthritis is presented.

METHODS

All the patients admitted to this study had "definite" or "classic" rheumatoid arthritis according to American Rheumatism Association criteria and had evidence of active disease.[8,9] Most of the patients were at the early stage of the disease. Their clinical progress was assessed by the following indices: (1) duration of morning stiffness (mins), (2) numbers of painful joints. (3) numbers of swollen joints, (4) grip strength (1b), (5) erythrocyte sedimentation rate (ESR) by the Westergren method, and (6) immunoglobulin IgG, IgA, IgM. The first four indices were recorded weekly and the last two indices recorded monthly. For monitoring toxicity, patients were regularly questioned about skin rash, epigastralgia, edema, diarrhea, bleeding tendency and other possible side effects. Hemoglobin, white blood cell count, platelet estimate, GOT, GPT, BUN, creatinine and urinalysis were monitored monthly.

Rentgenographic rheumatoid progression and functional capacity were assessed at the beginning and at the end of therapy in each patients according to A.R.A. (Steinbrocker).

The preparation consisted of coarse powder of Cinnamomi Ramulus, Paeoniae Radix, Zingiberis Rhizoma, Zizyphi Fructus, Glycyrrhizae Radix, Aconiti Tuber, Atractylodis Rhizoma, Poria in the ratio of 4:3:3:3:1.5:5:5:0.5. The drug was prepared by immersing 1 kg of the mixture in 5 L 50% alcohol and decocted in 60℃ hot water bath 4 times. The extracted solutions were mixed then evaporated and concentrated in a rotary vacuum evaporator at a temperature below 50℃. The extraction rate was 22%. All patients were treated with 6g of Gui-Lin-Tang daily, giving 2g orally after meal. Some patients who had been treated with gold or D-penicillamine previously were given Gui-Lin-Tang in combination. Gold and D-penicillamine were also given to the patients under Gui-Lin-Tang therapy but still with higher activity.

RESULTS

Table I summarizes the outcome of the Gui-Lin-Tang in the 44 patients studied. All of the markedly improved patients were female. All of the 8 patients treated with Gui-Lin-Tang in combination with gold had improvement. A 51-year-old female patient was withdrown from steroid dependence after having been treated with Gui-Lin-Tang and gold for 3 months. The mean values of eight clinical and laboratory parameters before and after treatment were shown in Table II. Duration of morning stiffness was not applicable to all the patients. The grip strength, articular indices by numbers of painful or swollen joints and ESR were considered the most useful criteria for assessing improvement

of rheumatoid activity. The grip strength measured by hand gripper, not by sphygmomanometer, was considered sensitive if the activity and articular damage were not very severe. Most of the mean values of the parameters were shown at abnormally lower levels in the group treated with Gui-Lin-Tang plus gold than the group treated with Gui-Lin-Tang alone. This was due to the higher rheumatoid activity in patients treated with Gui-Lin-Tang plus gold. Twenty-one patients (61.7%) in Gui-Lin-Tang group and 6 (75%) in Gui-Lin-Tang plus gold group showed improvement. Twenty patients (58.8%) in Gui-Lin-Tang group and 5 (62.5%) in Gui-Lin-Tang plus gold group showed increased grip strength. Twenty-five patients (73.5%) in Gui-Lin-Tang group and 8 (100%) in Gui-Lin-Tang plus gold group showed decreased numbers of painful joints. Eleven (34.3%) in 26 patients treated with Gui-Lin-Tang and 5 (62.5%) in 7 patients treated with Gui-Lin-Tang plus gold showed lower ESR values.

The average values of immunoglobulin were decreased in the group treated with Gui-Lin-Tang alone but not in the group treated with Gui-Lin-Tang plus gold. IgG in eight patients, IgA in 8 patients and IgM in 8 patients showed lower values in Gui-Lin-Tang group. IgG in two patients and IgA in 4 patients and IgM in 3 patients were showed decreased values in Gui-Lin-Tang plus gold group. Even the values of immunoglobulin were changed but most of them were still in normal range.

The improvements of functional capacity were showed in Table III. Most of the patients in Gui-Lin-Tang group had better functional capacity than those in Gui-Lin-Tang plus gold group before treatment. This was because the patients in the Gui-Lin-Tang group were at the early stage of the disease. The patients in both groups had increased functional capacity after treatment. The roentgenographic progress showed no change in most patients except one patient progressed from stage 2 to stage 3, and another one progressed from stage 1 to stage 2.

Hemoglobin, white count, GOT, GPT, BUN, creatinine and urinalysis were monitored but no toxic reaction was found in either group. There were some adverse side effects but they were tolerated. Two patients in Gui-Lin-Tang group and 3 in Gui-Lin-Tang plus gold had blurring of vision. Two patients in Gui-Lin-Tang group and 1 in Gui-Lin-Tang plus gold group had dry mouth sensation. One patient had prolonged menstruation, 1 had echymosis and 2 had skin itching in Gui-Lin-Tang treated group. Only one patient had skin rash in Gui-Lin-Tang plus gold group. The skin rash disappeared after the patient was treated with Gui-Lin-Tang without gold (Table IV).

DISCUSSION

Gui-Zhi-Tang, containing Cinnamomi Ramulus, Paeoniae Radix, Zingiberis Rhizoma, Zizyphi Fructus and Glycyrrhizae Radix has been administered as an antipyretics or antispasmodics by Chinese herb doctor since ancient time.

Modified formula of Gui-Zhi-Tang with prepared Fu Zi is used to treat windphobia, spasm which resulted in inability to stretch and contract the extremities, and other symptoms of chronic articular rheumatism.

Each component of Gui-Zhi-Tang has its own effect. Cinnamomi Ramulus, containing cinnamic aldehyde, is used as an antipyretics or diuretics. Paeoniae Radix, containing paeoniflorin, has antispasmodic, analgesic and circulatory enhancing effects. Zingiberis Rhizoma, containing zingiberol, enhances blood circulation and inhibit adjuvant arthritis in mice. Zizyphi Fructus, containing protein, sugar and vitamins, is a nutrient and a tonic. Glycyrrhizae Radix, containing glycyrrhizin, has antitoxic and anti-inflammatory effects but it may cause edema and hypertension if used too long. Glycyrrhizin can further decompose to glycyrrhetic acid and glucuronic acid in the body. Glycyrrhetic acid has an effect to lower the basal metabolic rate. Aconiti Tuber, containing hypaconitine and aconitine, has vasodilatation, antiinflammatory and cardiotonic effects but overdose may result in ventricular fibrillation. The effect of the formula is the sum effect of these component drugs.

Gui-Lin-Tang used in this study is adding Atractylodis Rhizoma and Poria to modified Gui-Zhi-Tang with Fu Zi to enhance the diuretic effect for removing the uric acid. Kano, et al reported the inhibition of adjuvant arthritis by Gui-Zhi-Tang.[7] Walksman, et al speculated that adjuvant arthritis was caused by cell-mediated or delayed immune reaction.[10] From the results of this study, it seems that the analgesic and edema inhibition of Gui-Lin-Tang is related to immune regulatory function in the body, and the Gui-Lin-Tang has the effect to inhibit immune function.

There was no summation effect after treating the patient by adding Gui-Lin-Tang in addition to gold. Further study is necessary to elucidate the cause.

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REFERENCES

1. Shiokawa Y. Immunotheraphy in rheumatoid arthritis. Pharma Medica 1987; 5:9–10.
2. Zvaifler NJ. Arthritis and allied conditions: etiology and pathogenesis of rheumatoid arthritis, ed 8. Philadelphia: Lea & Febiger, Publishers Inc, 1979: 417–426.
3. Tsang IK, Patterson CA, Stein HB, et al. D-penicillamine in the treatment of rheumatoid arthritis. Arthritis Rheum 1977; 20: 666–670.
4. Zuckner J, Ramsey RH, Dorner RW, et al. D-penicillamine in rheumatoid arthritis. Arthritis Rheum 1970; 13:131–138.
5. Cats A. A multiple controlled trial of the effect of different dosage of gold therapy, followed by a maintenance dosage. Agent and Action 1976; 6:355.
6. Kuwaki TH. Handbook of Chinese herb medication. Sogensha, Osaka, 1986:146.
7. Kano K, et al. Anti-inflammatory effect of Cinnamon, Atractylodes and Aconite combination. Oriental Healing Arts International Bulletin 1987; 12: 277–291.
8. Ropes Mw, Bennett GA, Cobb S, et al. 1958 revision of diagnostic criteria for rheumatoid arthritis. Bull Rheum Dis 1958; 9: 175–176.
9. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. JAMA 1949; 140:659.
10. Walksman BH, Wennessten C. Positive transfer of adjuvant arthritis in rats with living lymphoid of sensitized dornors, Int. Arch. Allergy Appl Immunol 1963; 23: 129–139.

Table I. Summary of the outcome of Gui-Lin-Tang treatment in 44 patients

	marked improvement	moderate or slight improvement	no improvement
Gui-Lin-Tang	7	18	9
Gui-Lin-Tang + Gold	5	3	0
Gui-Lin-Tang + D-penicillamine	0	1	1
Total	12	22	10

Table II. Mean value of clinical and laboratory parameters pre- and post-treatment

		Morning stiffness (min)	Sum grip strength of both hands (lb)	Painful joints	Swollen joints	ESR	IgG	IgA	IgM
GLT	pre-R	150 ± 30	51.8 ± 3.3	7.79 ± 0.78	5.29 ± 0.73	42.3 ± 7.6	1479 ± 182	346 ± 32	158 ± 25
	post-R	82.4 ± 26.8*	57.6 ± 3.7	3.56 ± 0.55***	1.5 ± 0.41***	41.5 ± 5.1	1382 ± 185	320 ± 33	141 ± 22
GLT & Gold	pre-R	128 ± 57	19.0 ± 3.8	15.4 ±3.3	8.75 ±2.53	69.4 ±19.7	1330 ±250	310 ±26	152 ±15
	post-R	49.4 ± 20.8	22.7 ± 20.8	2.50 ± 1**	1.13 ± 0.58*	47.1 ± 16.8	1356 ± 208	278 ± 25	155 ± 20

(1) GLT: Gui-Lin-Tang.

(2) Mean ± SE (n = 34 for GLT, 8 for GLT & Gold).

(3) *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ as analyzed by paired comparison student's t test.

Table III. Therapeutic classification before and after treatment with Gui-Lin-Tang

		Before treatment (No. of patients)		After treatment (No. of patients)	
		stage	class	stage	class
Gui-Lin-Tang	I	8	23	7	28
	II	22	10	23	6
	III	2	1	2	0
	IV	2	0	2	0
	Total	34	34	34	34
Gui-Lin-Tang & Gold	I	0	0	0	2
	II	3	6	2	4
	III	3	1	4	1
	IV	2	1	2	1
	Total	8	8	8	8

Table IV. Adverse reactions to Gui-Lin-Tang treatment

	Gui-Lin-Tang	Gui-Lin-Tang + Gold
Blurring vision	2	3
Dry mouth	2	1
Prolonged menstruation	1	0
Echymosis	1	0
Itching	2	0
Skin rash	0	1
Total	8	5

桂枝加苓朮附湯對類風濕性關節炎的療效之研究

周鉅文主任 謝明村所長 陳和昌主任 李毅醫師
中國醫藥學院北港附設醫院 中國醫藥學院中國藥學研究所

研究目的

本研究的目的在評估〝桂枝加苓朮附湯〞對於類風濕性關節炎的療效，並針對其消炎鎮痛效果及免疫學上的功能加以探討。

材料及方法

材料：

將桂枝、芍藥、生薑、大棗、甘草、附子、茯苓、白朮等八種藥材依4：3：3：3：1.5：0.5：5：5之比例混合均勻，取一公斤置於圓底燒瓶內，加入50%酒精5000ml，在60°C水浴回流連續抽取4次，收集全部抽取液過濾，於50°C下眞空減壓濃縮至呈黏稠狀，移置50°C烘箱完全乾燥，加入賦形劑，以電動磨粉機研成細粉。

方法：

1. 臨床研究：由中國醫藥學院北港附設醫院關節炎特別門診進行。
   (1)按美國風濕症學會1958年重訂的診斷標準，採Presenting sampling technique篩選出典型的(classic)及確定的(definite)類風濕性關節炎病人，作臨床療效的評估。
   (2)以Random number table將病人分爲A組和B組，A組中未接受正式抗風濕療法的患者直接給予桂枝加苓朮附湯，而曾接受其他抗風濕藥物治療者，則以二星期wash-out再給藥；B組病人給予桂枝加苓朮附湯與金劑或D-Penicillamine併用。
   (3)以Lansbury的關節炎activity index取joint score（包括疼痛和腫脹關節數）、morning stiffness持續時間(min)、握力(lb)、血球沈降率(mm/hr)作總合客觀的臨床評估。每二星期施行一次。
   (4)免疫學方面，一個月測試一次Rheumatoid factor, IgG, IgA, IgM,T-cell, B-cell做爲指標。
   (5)副作用及安全性方面，每六星期測試一次Hematocrit, WBC, BUN,Differential count，urine routine，SGOT.
2. 基礎藥理學研究：由中國醫藥學院中國藥學研究所進行。
   (1)鎮痛作用：以小白鼠利用熱板法、醋酸法、壓尾法等，測其正常之痛閾，再與給予桂枝加苓朮附湯後之痛閾比較。
   (2)協調作用，肌肉鬆弛之影響：以懸垂法測定桂枝加苓朮附湯對骨骼肌運動協調之影響。

(3)對中樞神經興奮劑引起的痙攣之影響：使用不同中樞神經興奮劑，誘發小白鼠產生痙攣，比較桂枝加芩朮附湯之抗痙攣作用。

(4)Evans Blue 色素擴散法對毛細血管抵抗性的測定：測定桂枝加芩朮附湯對於histamine，serotonin，bradykinin 等引起血管擴張，透過性亢進的炎性血管反應的原因物質之抑制作用。

(5)測定炎性反應的試驗：測定桂枝加芩朮附湯對於實驗性炎症的抑制反應，包括：①Formalin浮腫抑制試驗，②Carrageenin浮腫抑制試驗，③Dextran浮腫抑制試驗，④Adjuvant 關節炎抑制試驗。

研究結果

1. 44位(男11人，女33人)，典型的或確定的類風濕性關節炎患者中，34人用桂枝加芩朮附湯(A組)，8人用桂枝加芩朮附湯加金劑(B組)，2人用桂枝加芩朮附湯加D-Penicillamine 治療。全部患者平均服藥77.2天。由治療前後的參數得知顯效12人(27.2%) 均爲女性，22人(50%)有效，而10人(22%)無效。一位51歲女性患者以桂枝加芩朮附湯配合金劑治療三個月後，脫離對類固醇的依賴

2. 由臨床數據顯示，A組20人(58.8%)及B組5人(62.5%)握力强度增加；A組25人(73.5%)及B組8人(100%)疼痛關節數減少；A組26位中的11人(58.8%)及B組7位中的5人(62.5%)其ESR值降低。

3. 在免疫球蛋白方面，A組的IgG，IgA，IgM值降低者各有8人，而B組有2人之IgG，4人之IgA，3人IgM 值降低。即使免疫球蛋白數值產生變化，但多仍維持在正常範圍內。

4. 無論A組或B組，在治療後關節活動機能均增加，但X光檢查顯示除1人由StageⅡ變成StageⅢ，1人由StageⅠ變成StageⅡ外，其餘均無變化。

5. HB，WBC，GPT，GOT，Creatinine，Urinalysis 之監測顯示無毒性反應發生，雖有些不良副作用，但均在可忍受的範圍內。A組2人及B組3人視力模糊；A組2人及B組1人有口乾現象；A組中1人經期延長，1人瘀血，2人皮膚發癢：B組有1人產生皮疹，經撤除金劑後皮疹消失。

6. 基礎藥理學實驗如圖所示：大白鼠以0.1% Serotonin 0.1ml 右後肢足蹠皮下注射誘發浮腫，可見對照組於90分鐘時浮腫最嚴重；口服1.0g/kg 桂枝加芩朮附湯能緩解浮腫現象，於60分鐘時抑制作用最强，並且在誘發浮腫後30分鐘即呈現顯著的抑制浮腫作用。

Mean value of clinical and laboratory parameters pre- and post- treatment

		Morning stiffness (min)	Sum grip strength of both hands (lb)	Painful joints	Swollen joints	ESR	IgG	IgA	IgM
GLT	Pre-	150.0 ± 30.0	51.8 ± 3.3	7.79 ± 0.78	5.29 ± 0.73	42.3 ± 7.6	1479 ± 182	346 ± 32	158 ± 25
	Post-	82.4 ± 26.8*	57.6 ± 3.7	3.56 ± 0.55***	1.50 ± 0.41***	41.5 ± 5.1	1382 ± 185	320 ±33	141 ± 22
GLT & Gold	Pre-	128.0 ± 57.0	19.0 ± 3.8	15.40 ± 3.30	8.75 ± 2.53	69.4 ± 19.7	1330 ± 250	310 ± 26	152 ± 15
	Post-	49.4 ± 20.8	22.7 ± 20.8	2.50 ± 1.00**	1.13 ± 0.58*	47.1 ± 16.8	1356 ± 208	278 ± 25	155 ± 20

1) GLT: Gui-Lin-Tang. 2) Mean ± SE (n=34 for GLT, 8 for GLT & Gold).
3) * $P<0.05$; ** $P<0.01$; *** $P<0.001$ as analyzed by paired comparison student's t test.

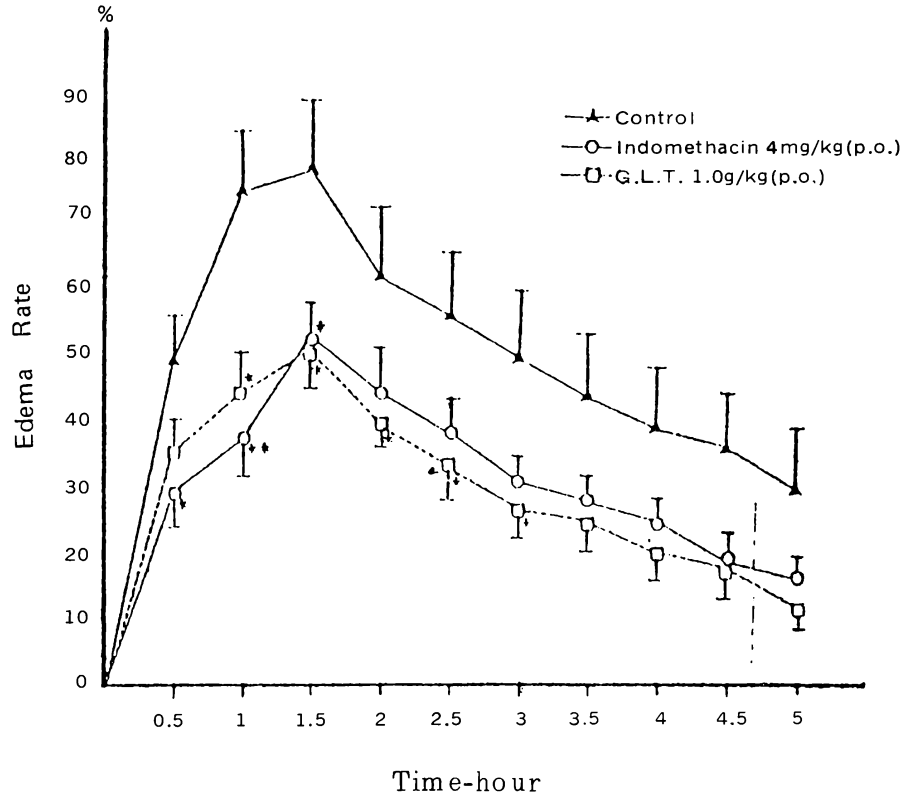

Figure 1. Anti inflammatory activity of Gui-Lin-Tang extracts on seroton in (0.1%) induced-edema in rats.
* $P < 0.05$, ** $P < 0.01$ (compared with control)

討 論

1. 桂枝湯(Gui-Zhi-Tang)是由桂枝、芍藥、生薑、大棗、甘草所組成，中醫師臨床用爲解熱劑及抗痙攣劑。
2. 桂枝湯加炮附子，則成桂枝加附子湯，中醫師臨床用於治療惡風，手脚拘急，不能屈伸，即當今之慢性類風濕性關節炎。其中：

⑴桂枝(Cinnamomi Ramulus)

主成分爲Cinnamic aldehyde，有解熱及利尿作用。

⑵赤芍(Paeoniae Radix)

主成分爲Paeoniflorin，有解痙、鎮痛及促進血循的作用。

⑶生薑(Zingiberis Rhizoma)

主成分爲Zingiberol，有促進血循及抑制大白鼠之蛋白性關節炎作用。

⑷大棗(Zizyphi Fructus)

主成分爲蛋白質、糖類及維生素，有補充營養作用。

⑸甘草(Glycyrrhizae Radix)

主成分Glycyrrhizin，在體內分解成Glycyrrhetic acid及Glucuronic acid，有解毒及抗炎作用，但長期服用會引起水腫和血壓升高，Glycyrrhetic acid 會降低基礎代謝。

⑹附子(Aconiti Tuber)

主成分爲Hypaconitine，Aconitine，有血管擴張、抗炎及强心作用，但過量會導致心室纖維顫動。

3. 桂枝加附子湯再加炒白朮與茯苓則成桂枝加芍朮附湯，目的是在增强利尿作用，以利尿酸之排泄。
4. 根據Walksman，et al等報告指出，adjuvant arthritis與Cell-mediated or delayed-immune reaction有關，而Kano，et al等研究顯示，桂枝加芍朮附湯能抑制adjuvant arthritis。
5. 由本實驗結果顯示，桂枝加芍朮附湯對於關節疼痛與腫脹有抑制作用，其原因可能與抑制免疫功能有關。
6. 桂枝加芍朮附湯與金劑併用後，抗關節疼痛與腫脹作用並無加强，其原因正在研究中。